Pre-Clinical Infection Models: Experimental and Clinical Data Supporting PK/PD Approaches

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PK/PD

Walking the tightrope between efficacy and toxicity

PK/PD Optimization

- Maximize Killing
- Minimize Resistance
- Exploit Differing Mechanisms of Action & PK/PD
- Minimize Toxicity

Optimize combination of antibiotics in difficult to treat infections based PK/PD strategies
Clinical Outcomes and Kill
Mortality and In Vitro Outcomes

Miyazaki et. al. AAC 2012.
Microbiologic Considerations in In vitro systems

• Strain Selection
• Bacterial Density
• Duration of Treatment
• Endpoint of study
• Resistance Plating and Drug Plates
• Time Course
Recommendations for Robust non-clinical data

Generating robust and informative nonclinical *in vitro* and *in vivo* bacterial infection model efficacy data to support translation to humans

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Screening Tools

Inhibitory Tools: Checkerboard

tps://doi.org/10.1371/journal.pone.0126479
In Vitro Pharmacodynamic Models
One Compartment and Hollow Fiber Infection Model
Studying Combinations
In Vitro Compartment Model


Blasser 1985
Colistin Mono Front-Loading: High-Dose Intensity Regimens toward COMBOS

Colistin vs. P. aeruginosa

Traditional: Patient Package
Insert Regimens and Clinically Achievable up to 2mg/L q24h

Higher Dosage Regimens:
- 4mg/L q24h
- 8mg/L q24h
- 6mg/L q24h x1 then 2mg/L q24h
Hollow Fiber Infection Model (HFIM)
Monotherapy Colistin: Rapid Amplification of Resistance in MDR *P. aeruginosa*

Monotherapy: Paradoxical Effect for Polymyxin B in A. baumannii

Polymyxin-heteroresistant Carbapenem-Resistant A. baumannii

Exploring Novel Dosing: Fusidic Acid
Front-Loading: High-Dose Intensity Regimens

600 mg q12h

1200 mg q12h on day 1, then 600 mg q12h

1500 mg q12h on day 1, then 600 mg q12h

CEM-101 (Fusidic Acid) vs. S. aureus
Phase II Dose Selected... Based on PK/PD Principles and Emergence of Resistance

How can we translate this to patients
Understanding development of resistance in a patient from an NIH Funded PK/PD/TD population study for CMS/Colistin.
Evolution of polymyxin-resistance toward complete Pandrug-Resistant A. baumannii

Recapitulation of colistin + meropenem patient 149 received in the clinical study

Evolution of polymyxin-resistance *A. baumannii*: HFIM-derived vs. patient-derived

![Graph showing the evolution of polymyxin resistance in patient and in vitro settings.](image)

Lenhard JR, Thamlikitkul V, Silviera FP, et al. Journal of Antimicrobial Chemotherapy. Accepted
“Among 17 patients who were treated for colistin-resistant *A. baumannii* infections, 15 received various CMS-based combination regimens. The most common regimen was a combination of CMS, a carbapenem, and ampicillin-sulbactam (n = 7). None of these 7 patients died within 30 days of the infection, within 30 days of the infection, compared with 6 of 10 (60%) patients who received other antimicrobial regimens (P = .03 by Fisher exact test).”

3-Drug Combination vs. nearly PDR A. baumannii from Patient 149: Complete eradication by 96h

03-149.2: $\text{MIC}_{\text{polyB}}=32$, $\text{MIC}_{\text{meropenem}}=64$, $\text{MIC}_{\text{Ampicillin/Sulbactam}}=32$

Combating Next Generation Resistance Mechanisms and Profiling Populations
Finding New Solutions for PDR Enterobacteriaceae

MCR1_NJ Plasmid: MCR-1, NDM-5

Finding New Solutions for PDR Enterobacteriaceae

Toward Molecularly Targeted PK/PD Strategies
PK/PD Targeting Molecular Mechanisms of Resistance

- NDM
  - Aztreonam

- ESBL CTX M-15
  - Ceftazidime
  - Avibactam
CAZ-AVI + Aztreonam = Synergy

Figure 2. Synergy between ceftazidime-avibactam and aztreonam (Etest)

CAZ-AVI + Aztreonam = Synergy

<table>
<thead>
<tr>
<th></th>
<th>ESBL</th>
<th>KPC</th>
<th>Metallo β-lactamase</th>
</tr>
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<tbody>
<tr>
<td>Piperacillin-Tazobactam</td>
<td>S</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>3rd Generation Cephalosporins</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazidime-Avibactam</td>
<td>S</td>
<td>S</td>
<td>R</td>
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<tr>
<td>Cefepime</td>
<td>I/R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>R</td>
<td>R</td>
<td>S</td>
</tr>
</tbody>
</table>
**In vertebrate models**

- **G. mellonella**, Larvae of wax moth, have been used to study pathogenicity

Colistin Alone <50% Survival

Colistin Combo 100% Survival

Hornsley et. al. AAC. 2012.
The Future: Tracking \textit{in vivo} Evolution (PNAS 2007)

![Diagram showing the evolution of bacterial strains over time]

**Table 1. Sequential appearance of 35 point mutations in the blood isolates**

<table>
<thead>
<tr>
<th>Date of isolation, month/day/year</th>
<th>Isolate</th>
<th>MIC, (\mu g/ml)</th>
<th>Numeric identifier of mutation$^\dagger$</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Vancomycin</td>
<td>Rifampin</td>
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<tr>
<td>7/20/2000</td>
<td>JH1</td>
<td>1.0</td>
<td>0.012</td>
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<tr>
<td>9/20/2000</td>
<td>JH2</td>
<td>4.0</td>
<td>16</td>
</tr>
<tr>
<td>10/1/2000</td>
<td>JH5</td>
<td>6.0</td>
<td>16</td>
</tr>
<tr>
<td>10/6/2000</td>
<td>JH6</td>
<td>8.0</td>
<td>16</td>
</tr>
<tr>
<td>10/13/2000</td>
<td>JH9</td>
<td>8.0</td>
<td>16</td>
</tr>
</tbody>
</table>

*E-test. $^\dagger$, Numbers 1–35 are assigned to mutations in the time order of their appearance. The presence of a mutation is indicated by $\bullet$, and the absence of a mutation due to possible reversion is indicated by $\circ$. ND, not determined. Mutations 34 and 35 between JH1 and JH9 were predicted to be in JH9 but could not be PCR sequenced (see SI Appendix for a discussion). $^\ddagger$, in \textit{bla}R7 on the plasmid; $^{\ast}$, in \textit{SA}1702 in the \textit{wva} operon; $\|$ in \textit{poB}; $\|$ in \textit{poC}; $^{**}$, in gene \textit{SA}1129 with unknown function; $^{\ddagger}$, in \textit{SA}1249; $^{\dagger}$, in \textit{agr}C in the \textit{agr} locus; $^{\ast}$, in \textit{yycF} in the \textit{yyc} gene cluster with \textit{yycF} and \textit{yycG}. \textit{SA}XXXX: N315 identifiers (17).
PK/PD Rabbit Infection Model

2 Rabbit Infection Models: Pneumonia and Tunnelled Silastic Vascular Catheter

**Efficacy:** Quantitative Culture in blood, lung, spleen, kidney and liver

**Toxicity:** Serum samples, histopathology
PK/PD studies greatly assisted development of these dosing guidelines
Inviting you ALL out to Join ISAP as a member
Our Annual Meeting - Here on Friday 4pm
isap.org
Alan Forrest and 10 Excellent Young
Investigator Talks on PK/PD
Mini non-alcoholic cocktail reception
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